2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

a1 cont

3. (Amended) An isolated nucleic acid molecule according to Claim 1 wherein said nucleotide sequence is a cDNA sequence.

RESPONSE

I. Status of the Claims

No claims have been canceled. Claims 1-3 have been amended. No new claims have been added.

Claims 1-4 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Amended Claims

Claim 1 has been amended to further clarify the claim. Support for this claim can be found throughout the specification as originally filed. Applicants state for the record that this revision is being made solely to advance the present case more rapidly to allowance, and does not in any way limit the scope of claim 1 as originally filed.

Claim 2 has been amended to further clarify the claim, and to recite that the hybridization conditions are highly stringent hybridization conditions. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 2 as originally filed and in the specification on page 4, lines 10-18.

Claim 3 has been amended to further clarify the claim. Support for this claim can be found throughout the specification as originally filed. Applicants state for the record that this revision is being made solely to advance the present case more rapidly to allowance, and does not in any way limit the scope of claim 3 as originally filed.

It will be understood that no new matter is included within the amended claims.

III. Oath/Declaration

The Action first objects to the oath or declaration as defective, as allegedly the citizenship of inventor number 3, Andrew Olson, is not provided. Applicants therefore submit herewith a new declaration of Andrew Olson.

IV. Claim Objection

The Examiner objects to Claim 1, based on the term "nucleotide sequence first disclosed in SEQ ID NO:1" (Action at page 2). Although Applicants submit that this term is sufficiently clear and definite, solely in order to more rapidly progress the present case to allowance, the complained of term has been removed from Claim 1. Applicants therefore respectfully request that the objection to Claim 1 be withdrawn.

V. Rejection of Claims 1-3 Under 35 U.S.C. § 101

The Action first rejects claims 1-3 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The Action gives a number of reasons for the alleged lack of utility. First, the Action states that "Applicant (*sic*) indicates neither the exact function of the protein encoded by SEQ ID NO:1 nor the function of the polypeptide of SEQ ID NO:2 in claims 1-3" (Action at page 3). Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). The Action goes on to state that the invention lacks utility because the disclosure provides no "guidance as to where the important structural elements of serine proteases such as the catalytic domain, binding domain and the like are located" (Action at page 3). This is also misplaced, as it is well established that "an inventor is not required to understand the theory of how his invention works". *Micro Motion, Inc. v. Exac Corp.*, 16 USPQ2d 1001, 1013 (Cal. 1990). The statement that "no working examples of polypeptides comprising the sequence of SEQ ID NO:2, nucleic acid molecules comprising SEQ ID NO:1, or nucleic acids comprising at least 24 nucleotides of SEQ ID NO:1 are set forth in Applicant's (*sic*) disclosure" is also misplaced. It has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962).

The Examiner cites Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action states "Applicant's (*sic*) amino acid sequence SEQ ID NO:2 has, at best, 31.4% sequence identity with

an epidermis specific serine protease. Applicant's (sic) nucleic acid sequence SEQ ID NO:1 has no more than 14.5% nucleic acid sequence homology to the polynucleotide encoding a serine protease (see attached sequence alignments), which is significantly less than Bork's 70%" (action at page 4). However, this statement is wrong on at least two fronts. First, Applicants have not asserted that SEQ ID NO:1 is even an epidermis specific serine protease (particularly given the fact that the expression information in the specification on page 3, lines 6-10 indicates that Applicants' sequence is expressed in numerous non-epidermal tissues), let alone the specific epidermis serine protease that the Examiner used for the sequence comparisons (particularly given the fact that the epidermis specific serine protease used by the Examiner is from Xenopus, while Applicants' sequence is a human sequence), so these direct sequence comparisons are completely misplaced. Second, and even more importantly, the 70% figure cited from the Bork article relates to the 70% accuracy of the resulting prediction, not 70% homology. In fact, nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, and thus does not support the alleged lack of utility for the present invention.

Furthermore, Applicants would like to invite the Examiner's attention to the fact that a sequence sharing 99% percent homology over an extended region with the described sequence is present in the leading scientific repository for biological sequence data (GENBANK), and has been annotated by third party scientists *wholly unaffiliated with Applicants* a sequence "similar to epidermis specific serine protease" from humans (GenBank accession number XM_093852). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. In the present instance, the Examiner has argued that those skilled in the art would not believe that a protein has a given biochemical activity if it displays less than 70% homology with related proteins annotated as having that activity. First, even if, *arguendo*, one accepts the Examiner's contention that greater than 70% homology is required for one skilled in the art to believe that a sequence encodes a certain activity, the presently claimed sequence has exceeded the Examiner's, albeit arbitrary, threshold of sequence relatedness. Second, those skilled in the art would clearly believe that Applicants' sequence is a serine protease, as such a protein has been annotated by those skilled in the art as a serine protease. Given these indisputable facts, there can be no question that those skilled in the art clearly believe that the described sequences are serine proteases, and thus the Examiner's utility rejection must fail as a matter of law.

The Examiner next cites Smith and Zhang (Nature Biotechnology *15*:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous"

(Action at page 4). However, the Smith and Zhang article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first paragraph, emphasis added). Thus, Smith and Zhang do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner next cites Brenner (TIG *15*:132-133, 1999) as teaching that "most homologs must have different molecular and cellular functions" (Action at page 4). However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants. Thus, the Brenner article also does not support the alleged lack of utility.

Finally, the Examiner cites Broun *et al.* (Science *282*:1315-1317, 1998) and Van de Loo *et al.* (Proc. Natl. Acad. Sci. USA *92*:6743-6747, 1995) as teaching that prediction of function based on homology is unpredictable. However, these papers cite only one example, microsomal oleate desaturase/oleate 12-hydroxylase, where function based on sequence homology proved to be incorrect. One example out of the thousands of predictions of function based on homology that exist in the art is hardly indicative of a high level of uncertainty, and thus also does not support the alleged lack of utility.

Rather, the question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs.*

Chakrabarty, 206 USPQ 193 (S.Ct. 1980)).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The present invention has a number of substantial and credible utilities, one of which, as the specification details on page 5, lines 19-21, is that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos.

5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences are clearly related to human proteases, as detailed throughout the specification. The specification also teaches that proteases are associated with a wide variety of cellular functions, such as "regulating development, modulating cellular processes, fertility and infectious disease" (specification at page 1, lines 26-28). Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (C.C.P.A. 1964); *In re Malachowski*, 189 USPQ 432 (C.C.P.A. 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequences provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequences define how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of the Venter *et al.* article (Science, 2001, *291*:1304 *at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequences define biologically validated sequences that provide a unique and specific resource for mapping genome essentially as described in the Venter *et al.* article Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Yet another example of the utility of the present invention is in expanding the utility of data coming from the human genome project. Persons of skill in the art, as well as thousands of venture

capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. All current therapeutics used in humans directly or indirectly interact with biological sequences encoded by the human genome, and virtually all future human therapeutics shall do likewise. Consequently, billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-3 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

VI. Rejection of Claims 1-4 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

First, Applicants note for the record that claim 4 was not subject to a rejection under 35 U.S.C. § 101 (see Section V above and page 2 of the Action). Therefore, the present rejection of claim 4 under 35 U.S.C. § 112, first paragraph, as allegedly not supported by a specific, substantial, and credible utility or a well-established utility cannot stand.

Applicants submit that as all of the present claims, including claims 1-3, have been shown to have "a specific, substantial, and credible utility", as detailed in section V above, the present rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VII. Rejection of Claims 1-3 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claims 1-3 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action rejects claim 1 as allegedly indefinite based on the term "NHP". While Applicants submit that the term does not render the claim indefinite, the term "NHP" has been removed from the claim. Applicants state for the record that this amendment is made solely in order to progress the case more rapidly to allowance. Applicants therefore request withdrawal of this rejection.

The Action next rejects claim 2 as allegedly indefinite based on the term "stringent hybridization conditions", because the specific hybridization and washing conditions are not recited in the claim. Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). However, while Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance the claim has been revised to specifically recite "highly" stringent hybridization conditions. As the specification provides specific teaching regarding "highly stringent hybridization conditions", at least at page 4, lines 10-18, Applicants submit that revised Claim 2 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request withdrawal of this rejection.

The Action next rejects claim 3 as allegedly indefinite based on the term " wherein said nucleotide sequence is present in cDNA". While Applicants submit that the term is sufficiently definite, this term has been even further clarified to "wherein said nucleotide sequence is a cDNA sequence", which even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph.. Applicants therefore request withdrawal of this rejection.

VIII. Rejection of Claim 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the

art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the ... nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the

genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising at least 24 contiguous bases from SEQ ID NO:1 are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claim 1 thus meets the written description requirement.

For each of the foregoing reasons, Applicants submit that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, has been overcome, and request that the rejection be withdrawn.

IX. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Ramirez have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

March 1, 2002
Date

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Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 09/854,844

1. (Amended) An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:1.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

3. (Amended) An isolated nucleic acid molecule according to Claim 1 wherein said nucleotide sequence is a cDNA sequence.

4. An isolated nucleic acid molecule according to Claim 3 encoding the amino acid sequence described in SEQ ID NO:2.

Exhibit B

Marked Up Version of Amended Claims in U.S. Patent Application Ser. No. 09/854,844

1. (Amended) An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence [first disclosed in the NHP sequence described in] from SEQ ID NO:1.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

3. (Amended) An isolated nucleic acid molecule according to Claim 1 wherein said nucleotide sequence is [present in] a cDNA sequence.

4. An isolated nucleic acid molecule according to Claim 3 encoding the amino acid sequence described in SEQ ID NO:2.